August 16, 2004

Ken Nitschke
Technical Contact
Dow Chemical Company
1691 North Swede
Midland, MI 48674

Dear Mr. Nitschke:

The Office of Pollution Prevention and Toxics is transmitting EPA's comments on the robust summaries and test plan for Cycloaliphatic Epoxy Resin ERL-4221 posted on the ChemRTK HPV Challenge Program Web site on February 12, 2004. I commend Dow Chemical Company for its commitment to the HPV Challenge Program.

EPA reviews test plans and robust summaries to determine whether the reported data and test plans will provide the data necessary to adequately characterize each SIDS endpoint. On its Challenge Web site, EPA has provided guidance for determining the adequacy of data and preparing test plans used to prioritize chemicals for further work.

EPA will post this letter and the enclosed comments on the HPV Challenge Web site within the next few days. As noted in the comments, we ask that Dow advise the Agency, within 60 days of this posting on the Web site, of any modifications to its submission. Please send any electronic revisions or comments to the following e-mail addresses: oppt.ncic@epa.gov and chem.rtk@epa.gov.

If you have any questions about this response, please contact Dr. Ralph Northrop, of the HPV Chemicals Branch, at 202-564-7666. Submit questions about the HPV Challenge Program through the "Contact Us" link on the HPV Challenge Program Web site pages or through the TSCA Assistance Information Service (TSCA Hotline) at (202) 554-1404. The TSCA Hotline can also be reached by e-mail at tsca-hotline@epa.gov.

I thank you for your submission and look forward to your continued participation in the HPV Challenge Program.

Sincerely,

/s/

Oscar Hernandez, Director
Risk Assessment Division

Enclosure

cc: W. Penberthy
M. E. Weber

EPA Comments on Chemical RTK HPV Challenge Submission:
Cycloaliphatic Epoxy Resin ERL-4221

SUMMARY OF EPA COMMENTS

The sponsor, The Dow Chemical Company, submitted a test plan and robust summaries to EPA for Cycloaliphatic epoxy resin ERL-4221, CAS No. 2386-87-0, dated December 23, 2003. EPA posted the submission on the ChemRTK HPV Challenge Web site on February 12, 2004.

EPA has reviewed this submission and has reached the following conclusions:

1. Physicochemical Properties. The data provided by the submitter for melting point, boiling point, and vapor pressure are adequate for the purposes of the HPV Challenge Program. The reported measurements of partition coefficient and water solubility were complicated by competing hydrolysis reactions, and estimated values are preferred.

2. Environmental Fate. The submitter needs to provide more information in its hydrolysis robust summary.

3. Health Effects. The submitted data are adequate for the purposes of the HPV Challenge Program. The submitter needs to address some deficiencies in the robust summaries.

4. Ecological Effects. The submitted fish and algal toxicity data are adequate for the purposes of the HPV Challenge Program. EPA reserves judgement on the adequacy of invertebrate data pending submission of critical information for the submitted study.

EPA requests that the submitter advise the Agency within 60 days of any modifications to its submission.

EPA COMMENTS ON THE CYCLOALIPHATIC EPOXY RESIN ERL-4221 CHALLENGE SUBMISSION

Test Plan

Physicochemical Properties (melting point, boiling point, vapor pressure, partition coefficient and water solubility)

The data provided by the submitter for melting point, boiling point, and vapor pressure are adequate for the purposes of the HPV Challenge Program.

The reported measurements of partition coefficient and water solubility were complicated by the competing hydrolysis reactions (see Environmental fate section).

Partition coefficient. The submitter did not discuss how hydrolysis could affect the log K_{ow} determination. EPA estimated a value of 2.37. This value is higher than the measured value, probably owing to hydrolysis during the test. Use of the estimated value for this endpoint is preferred in this case.

Water solubility. EPA found a water solubility of 0.03% (w/w) at 25 °C (approximately 300 mg/L) reported in Patty's Toxicology and obtained an estimated water solubility of 1,200 mg/L using WSKOW v1.41. The submitter's measured value of 13,850 mg/L after 18 d. is not consistent with either value. The submitter noted the apparent hydrolysis during the test but did not comment on its relevance to the reported result (the hydrolysis products are expected to be more water soluble). The lower values are more reasonable in this case.

Environmental Fate (photodegradation, stability in water, biodegradation, fugacity)

The data provided by the submitter for photodegradation, biodegradation, and fugacity are adequate for the purposes of the HPV Challenge Program.

Stability in water. The submission provided concentration data for only the initial and final (72 hr) concentrations. From the percent loss after 72 hours, the submitter calculated a half-life assuming first-order kinetics. According to OECD Guideline 111, first-order behavior should be tested by analyzing each reaction solution (pH 4, 7, and 9) at time intervals that provide a minimum of six spaced data points, normally between 20 and 70% of hydrolysis. The submitter also did not state what analytical method was used to follow the reaction. In the test plan, the submitter stated hydrolysis of ERL-4221 will result in cleavage of the ester linkage and opening of the epoxide rings; however, no analytical data were provided for the degradation products. Since the sponsored substance has three hydrolyzable groups, an ester and two epoxides, incomplete hydrolysis can yield up to five products in addition to the two completely hydrolyzed products; analysis of the products is needed to provide insight into the hydrolysis pathway and the aquatic toxicity test results. The submitter needs to provide more details on what was measured and what hydrolysis products were identified and/or measured.

Health Effects (acute toxicity, repeated-dose toxicity, genetic toxicity, and reproductive/developmental toxicity)

The submitted data are adequate for the purposes of the HPV Challenge Program. The submitter needs to address some deficiencies in the robust summaries.

Genetic toxicity. In the test plan, the reported negative results for the sister chromatid exchange assay in CHO cells need to be revised to reflect the statistically significant positive response reported in the robust summary.

Ecological Effects (fish, invertebrates, and algae)

The submitted fish and algal toxicity data are adequate for the purposes of the HPV Challenge Program. EPA reserves judgement on the adequacy of invertebrate data pending submission of critical information for the submitted invertebrate study.

Invertebrate. The following issues need to be addressed: (1) although this chemical has a hydrolysis half-life of 47hr, the 48-hr measurement showed no loss of chemical in a purported static test; (2) an extremely high water hardness was reported (609 mg/L $CaCO_3$); (3) the abnormal dose response at higher concentrations. If the submitter cannot resolve these issues, the invertebrate testing should be redone, with reported results based on flowthrough measured concentrations.

Specific Comments on the Robust Summaries

Health Effects (acute toxicity, repeated-dose toxicity, genetic toxicity, and reproductive/developmental toxicity)

Repeated-dose toxicity. The robust summary for the 90-day repeated-dose toxicity study (Padgett, 2001) is missing details including age of animals at study initiation; list of organs weighed at necropsy; list of tissues examined microscopically; results of statistical analyses and statistical significance of treatment-related findings.

Genetic toxicity. The robust summary for the reverse mutation assay in *Salmonella typhimurium* and *Escherichia coli* (Machigaki et al., 1995) is missing details including information on statistical analysis and level of statistical significance, and criteria for evaluating a positive or negative response.

Developmental toxicity. The robust summary for the prenatal developmental toxicity study (Varsho, 2003) is missing the following critical details: information on statistical methods and levels of significance; the proportion of fetuses evaluated for external, visceral and skeletal malformations; the magnitude of changes in maternal body weight/body weight gain; maternal kidney weight; fetal body weight; and litter incidence data for skeletal variations.

Followup Activity

EPA requests that the submitter advise the Agency within 60 days of any modifications to its submission.